N4 Pharma plc

Utilising its available unissued headroom, N4 Pharma has raised £0.35m (gross) new funding through an equity placing priced at 1.0p/share. Ensuring no distraction of existing resources destined for ongoing Nuvec® work, this will pay for the acquisition of a 71.25% stake in UK-based Nanogenics Limited ('the Company'), which reduces to 63.75% upon management's future vesting of shares for meeting key strategic milestones, along with a £50k 2-year discretionary loan (at base rate). As a result, N4P will now assume responsibility for overseeing completion of preclinical development for the Company's lead candidate, ECP105, over the coming 12–15 months, while also moving its proprietary non-viral delivery technology, LipTide®, toward validation. Having already recorded positive preliminary data for delivery of siRNA using LipTide®, with efficacy *in vivo* for prevention of glaucoma surgery failure, N4P's Directors believe this could lead relatively rapidly to first-in-human clinical trials. Furthermore, there is potential to identify technical synergies and complementarity through joint investigative programmes that utilise Nuvec®. Given the strong market and investor focus on the delivery of RNA therapy that followed the success of COVID vaccines, preclinical and clinical validation is expected to open up third party partnering/licencing opportunities for both platforms while also generating external interest for its innovative ophthalmic studies that identify significant unmet need. Having negotiated such a low price for Nanogenic's deep IP, which in-turn effectively doubles (or more) the Group's potential routes to commercial success, the shares appear to have been unduly punished by yesterday's announcement.

Use of Funds – Acquisition followed by preclinical development

From the £0.35m (gross) raised, £0.25m will be used to subscribe for an initial economic interest of 71.25% in Nanogenics, which reduces to 63.75% upon future shares vesting by management for meeting key strategic milestones. In addition, the Group is providing a loan facility of £50,000 to the Company (being a 2-year discretionary facility at base rate repayable before any dividends are paid by the Company) while also covering transaction costs.

Completion of Nanogenics' preclinical project work for ECP105 over the coming 12-15 months is expected to deliver the following advances:

- Identified optimal lead formulation/siRNA sequence
- Demonstration of *in vivo* efficacy
- Transferred manufacture from manual lab process to GMP-compatible microfluidics platform
- Generated additional/new IP
- FDA pre-IND and EMA/MHRA guidance discussions
- Be ready for rapid progress into GLP pre-clinical regulatory safety studies (outsourced CRO)

LipTide® - Proprietary delivery technology

Nanogenics is a research-based biotechnology company that specialises in the development of bespoke, peptide-based vectors for gene therapy. Recognising that one of the principal issues holding back therapeutic development in this area continues to be the inability to deliver nucleic acids

Stock Data

Share Price	1.05p
Market Capitalisation	£2.82m*
Shares in issue:	268.78m*
52 week high/low	3.80p/0.93p

**post-Placing numbers*

Company Profile

Sector:	Pharmaceuticals
Ticker:	N4P
Exchange:	AIM

Activities

N4 Pharma plc ('N4 Pharma', 'N4P' or 'the Group') is a specialist pharmaceutical company developing a novel silica nanoparticle delivery system for vaccines and therapeutics for licensing to pharmaceutical and biotech partners.

www.n4pharma.com

5-year share price performance

Source: LSE

Past performance and forecasts are not a reliable indicator of future results.

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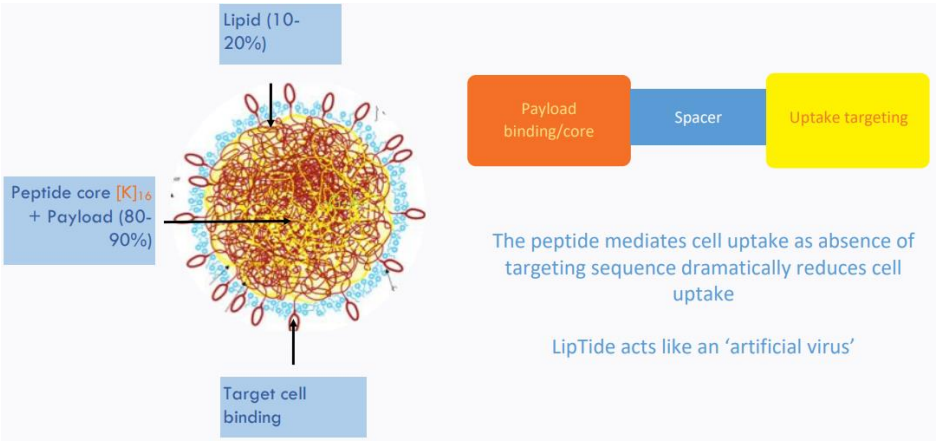
into target cells with efficiency, specificity and minimal side effects, it sought to address this major challenge through the development of Liptide®. Liptide® is a patented custom-built delivery system with unique construction, comprising a synthetic nanoparticle largely composed of peptides that was invented to mimic a natural virus for targeted delivery of RNA into cells. It takes the form of a peptide and lipid-based nanoparticle that has already demonstrated good *in vivo* efficacy across a range of models and delivery routes, including nebulised and systemic administration. The nanoparticle's peptide component performs two functions: binding the payload to form the core of the nanoparticle while also triggering receptors on target cells, causing it to be absorbed.

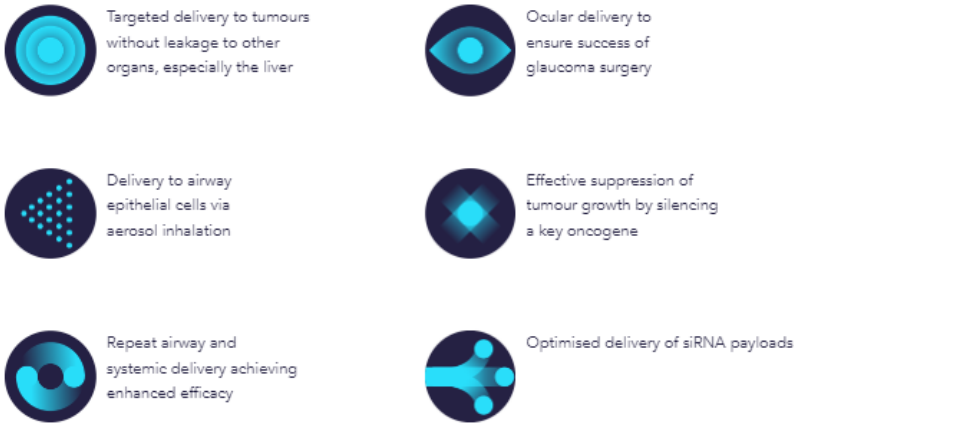
LipTide® Delivery Platform



Source: N4 Pharma, Investor Presentation, September 2023

This targeted, receptor-mediated, active uptake means that LipTide® can be used to deliver any type of nucleic acid payload, including siRNA, mRNA gene editing tools and vaccines. Once inside the cell, its lipid component then permits rapid and efficient endosomal release. As such, LipTide® technology offers new promise across several therapeutic areas of unmet need, while utilising a range of administration methods, including injection into the bloodstream, inhalation into the lungs and ocular passageways. Having successfully delivered across a range of applications *in vivo*, the next step for is to complete platform validation/create additional IP for the delivery system through clinical trials.

LipTide® - Unique Delivery System



Source: Nanogenics

Targeted delivery holds the key to LipTide®'s groundbreaking potential, providing:

Source: Nanogenics

Glaucoma commercial opportunity - Market exceeded US$5.5 billion in 2021

In 2020, more than 75 million people worldwide were affected by glaucoma. Being the leading cause of irreversible blindness, the condition's growing prevalence was highlighted in a February 2022 report by Global Market Insights that estimated the 2021 global glaucoma treatment market[2] exceeded US$5.5bn, with a projected 3.2% CAGR between 2022 and 2028.

Factors affecting this growth include:

- Advancements in therapeutic interventions
- Rising patient pool of geriatric population
- Increased clinical trials
- Increased awareness of eye care/earlier diagnosis

In fact, the therapeutic opportunity potentially goes well beyond just glaucoma. Myocardin-Related Transcription Factors ('MRTF') are also linked to additional fibrotic indications, including kidney[1], lung and liver[3]. MRTF, which upon actin polymerization translocates to the nucleus and binds to its cognate partner, serum response factor ('SRF'). The MRTF/SRF complex then drives a large cohort of genes involved in cytoskeleton remodelling, contractility, extracellular matrix organisation and many other processes. Accordingly, MRTF, activated by a variety of mechanical and chemical stimuli, affects a plethora of functions with physiological and pathological relevance. These include cell motility, development, metabolism and thus metastasis formation, inflammatory responses and predominantly-organ fibrosis.

This highlights the continuing unmet need for non-viral delivery vehicles for ophthalmology and beyond for both RNA and DNA payloads[4]. Nanogenics Directors consider LipTide® may offer such potential and that ECP105's development provides opportunity for both a significant commercial product while also validating the delivery platform. N4P moreover consider additional well-designed, low cost, *in vivo* PoC studies may be the ideal means to demonstrate LipTide®'s capabilities looking beyond just fibrosis (into areas including nucleic acid vaccines/CAR-T/airway delivery).

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8199744/

[2] https://www.gminsights.com/industry-analysis/glaucoma-treatment-market

[3] *Hetzler PT 3rd, Dash BC, Guo S, Hsia HC. Targeting Fibrotic Signaling: A Review of Current Literature and Identification of Future Therapeutic Targets to Improve Wound Healing. Ann Plast Surg. 2019 Dec;83(6):e92-e95. doi: 10.1097/SAP.0000000000001955. PMID: 31246672; PMCID: PMC6851445.*

[4] *Nucleic acid delivery: Are you developing what Big Pharma seeks? By Dr. Daniel Sieiro & Richard A. Brown September 20*

ECP-105 – Proprietary siRNA sequence using LipTide® for treatment after glaucoma surgery

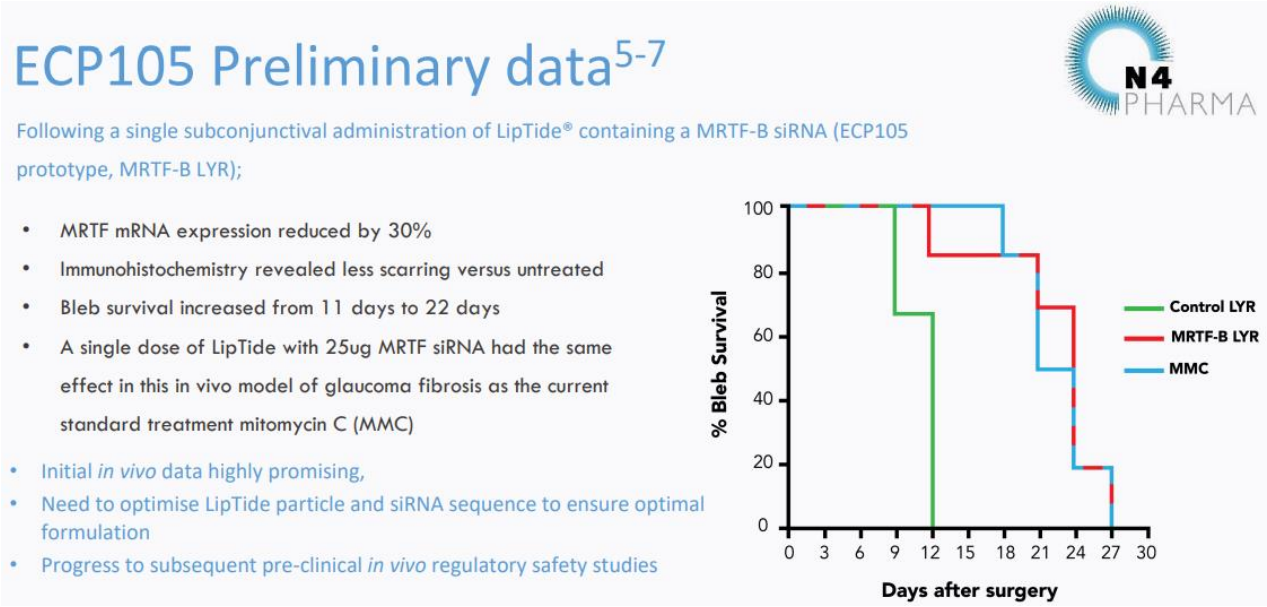
Trabeculectomy is a key surgical procedure used to treat glaucoma. In the absence of antifibrotic therapy, the failure rate can be up to 74% and, even with the use of 5-fluorouracil, failure rates are around 50% after five years. The current preventive measure against the fibrosis is to use, untargeted, cytotoxic anti-fibrotic drugs (e.g., Mitomycin C, a chemotherapy drug) which have a poor safety profile and are used off-label in the US market. New, safe, non-toxic and efficacious treatments are therefore urgently required to ensure the benefits of trabeculectomies are not just temporary (necessitating common repeat surgery to re-introduce the drain reservoir (or 'bleb')).

One such route may be found through silencing the Myocardin-Related Transcription Factors/Serum Response Factor ('MRTF/SRF') pathway, which significantly decreases matrix contraction, fibroblast protrusive behaviour, matrix degradation, and MMP gene expression in fibrotic human conjunctival fibroblasts. A report published in The Lancet on 25 February 2016, for example, noted that MRTF and SRF silencing with siRNAs decreased matrix contraction in fibrotic conjunctival fibroblasts by 80% and 87%, respectively; knocking down MRTF also significantly reduced the fibroblast dynamic index from 0·66 to 0·19 ($p<0·0001$), while decreasing matrix degradation from 0·87 to 0·33 ($p=0·006$) and downregulating the expression of key matrix metalloproteinases genes such as MMP1, MMP2, MMP9, and MMP14 ($p<0·05$).

Positive preliminary data

Nanogenic's ECP-105 is a promising breakthrough anti-fibrotic therapy to improve surgical outcomes and reduce re-admission rates for patients with severe glaucoma. *In vitro* proof of concept demonstrated siRNA inhibition of proteins related to fibrosis and ophthalmic indications. Subsequent single subjunctive administration of LipTide® containing a MRTF-B siRNA (ECP105 prototype, MRTF-B LYR), produced positive preliminary data for delivery and efficacy *in vivo* for prevention of glaucoma surgery failure, based on increased 'bleb' survival and decreased scarring underneath the surface of the eye without toxic side effects. Follow-on work will focus on generating new IP relating to (i) Novel bi-species (rabbit/human) siRNA sequences and, (ii) Formulation methodology/final product formulation/intended use of ECP105.

ECP105 Preliminary Data Following Administration of Liptide®



Source: N4 Pharma, Investor Presentation, September 2023

[5] Fernando O, Tagalakis AD, Awwad S, Brocchini S, Khaw PT, Hart SL, Yu-Wai-Man C. Development of targeted siRNA nanocomplexes to prevent fibrosis in experimental glaucoma filtration surgery. Mol Ther. 2018;26(12):2812-22.
[6] Sanghani, Amisha et al. "Novel PEGylated Lipid Nanoparticles Have a High Encapsulation Efficiency and Effectively Deliver MRTF-B siRNA in Conjunctival Fibroblasts." Pharmaceutics vol. 13,3 382. 13 Mar. 2021, doi:10.3390/pharmaceutics13030382
[7] Grover, Davinder S et al. "Historical Considerations and Innovations in the Perioperative Use of Mitomycin C for Glaucoma Filtration Surgery and Bleb Revisions." Journal of glaucoma vol. 29,3 (2020): 226-235. doi:10.1097/IJG.0000000000001438

ECP 105 Next Steps – Move into First-in-Human studies

Following satisfactory completion of *in vivo* GLP-toxicity regulatory studies, preparatory work to move ECP105 to First-in-Human studies can commence during its initial 12-months of funding:

- Gathering quotes from leading CROs (CRL/Charles River, etc.)
- Developing a Statement of Works ('SoW')
- Sourcing components and manufacturing pathway for ECP105 (GMP compliant)
- Seeking EMA/FDA advice on pre-clin study and our proposed trial designs

Subsequent First-in-Human studies follow-on steps would likely include:

- Transfer manufacture and source components to GMP
- Prepare IB/IMPD
- MHRA/EMA/FDA meetings/advice
- Submit Clinical Trial Application ('CTA')
- Start trial, 6-month dosing with up to a year follow up

N4P Finances - Runway sufficient to take it to the start of H2 2024

TPI estimates that the acquisition of Nanogenics will lift the Group's cash burn from a little over £100k/month during H1 2023 to around £130k/month going forward. With c.£1.29m cash/cash equivalents in the Group's balance sheet at end-June 2023, there appears to be runway sufficient to take it to the start of H2 2024 based on current programmes/schedules, although any decision to ramp- up of development for either of its delivery platforms or its new key preclinical candidate will likely bring this timetable closer.

Commercialisation Strategy - Focusing on strong commercial point of difference

Having already refined its near-term commercial strategy in order to highlight Nuvec®'s specific point of difference as a carrier of multiple siRNA compounds, the majority acquisition of Nanogenics now introduces a highly complementary but differentiated non-viral delivery technology along with a lead candidate that appears capable of securing a relatively quick route to clinic. Importantly, this opens opportunities to identify technical synergies through parallel development programmes involving both delivery platforms, while preclinical and clinical validation could open up third party licencing opportunities either individually or for both.

This is particularly exciting given that Nuvec® has already demonstrated ability to deliver multiple siRNA into the same cell, therein providing a unique solution for combination therapy treatments. Given that many drug development companies are presently undertaking early-phase pre-clinical/clinical testing/trials, they are generally more open to new, novel solutions than those at more advanced stages. Following its signing of two Material Transfer Agreements ('MTAs') back in 2021, one of which was a with major company in gene therapy and the second with a company developing its own DNA Covid vaccine, this work continues while the Group seeks further such partnership opportunities and, as such, the pace of progress here is largely determined by N4P's partner's own R&D work and drug launches.

Based on feedback from the patent examiner and further work the Group has already completed, it has been demonstrated that combining Nuvec® with adenoviral vectors (in addition to its earlier work on lentiviral vectors) can lead to an improvement in vector performance and a reduction in the amount of the viral vector required. Accordingly, it is presently pursuing patent applications in Europe (including UK); USA; Japan; India and Canada (and intends to file similar applications in Australia and China in due course) which, if granted, would be in addition to those already exclusively licensed from the University of Queensland ('UQ') in an effort to further strengthen the commercial protection of the delivery system. N4P is also exploring next generation use for oral delivery plus potential improvement in the application of viral vectors. Positive preliminary results from ongoing studies undertaken at UQ demonstrate orally delivered Nuvec® is capable of transfecting cells in the small intestine. The next step in this work is for UQ to repeat the success of this through an *in vivo* study, which management understands will be undertaken shortly.

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